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16. ABSTRACT

Pre- and postweaning measures of learning and locomotor activity were used as indices of CNS function after early perinatal neurotoxic insult. Triethyltin (0.0, 3.0, or 6.0 mg/kg, ip) administered on Postnatal Dat 5 (PND5) was used as the neurotoxicant. Learning deficits and alterations in locomotor activity were observed during both the pre- and postweaning periods. Preweaning learning ability was evaluated with an appetitive alleyway paradigm, while an automated radial-arm maze (RAM) was used to assess juvenile learning. Preweaning open-field locomotion was evaluated in the presence and absence of home-cage litter while postweaning activity was measured in an automated device, the Motron, or as a component of performance in the RAM. The 6.0-mg/kg TET-exposed animals requied more trials to acquire the alleyway task. RAM subjects receiving 6.0 mg/kg of TET were less accurate than those given 3.0 mg/kg or vehicle control. TET did not affect open-field activity on PND10; low levels of spontaneous locomotion occurred regardless of treatment. On PND13, there was a dose-related decrease in locomotion over home-cage litter while all groups exhibited equivalent low rates of locomotion in the absence of home-cage cures. All treatment groups were more active when tested over litter than over no litter. In contrast, on PND21 and throughout the RAM testing period, TET-exposed subjects exhibited dose-related increases in activity. TET produced treatment-related decreases in wet weight of whole brain, hippocampus, and cerebellum in both developing (PND23) and adult (PND200) animals with the hippocampus being most affected on a percentage basis. In contrast, no treatment-related body weight differences were observed at these times. The neurotoxocity of TET can be demonstrated during the preweaning period whether a commonly used endpoint in assessing CNS function (locomotor activity) is monitored or a more complex endpoint (learning) is evaluated provided (1) the method used to monitor locomotor activity incorporates both the normally low levels of preweaning locomotion and the more elevated levels induced by home-cage cues and (2) the learning paradigms utilized are more appropriate for the capabilities of the animal.

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Pre- and Postweaning Indices of Neurotoxicity in Rats: Effects of Triethyltin (TET)[1]

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Pre- and Postweaning Indices of Neurotoxicity in Rats: Effects of Triethyltin (TET). MILLER, D. B. (1984). *Toxicol. Appl. Pharmacol.* 72, 557–565. Pre- and postweaning measures of learning and locomotor activity were used as indices of CNS function after early perinatal neurotoxic insult. Triethyltin (0.0, 3.0, or 6.0 mg/kg, ip) administered on Postnatal Day 5 (PND5) was used as the neurotoxicant. Learning deficits and alterations in locomotor activity were observed during both the pre- and postweaning periods. Preweaning learning ability was evaluated with an appetitive alleyway paradigm, while an automated radial-arm maze (RAM) was used to assess juvenile learning. Preweaning open-field locomotion was evaluated in the presence and absence of home-cage litter while postweaning activity was measured in an automated device, the Motron, or as a component of performance in the RAM. The 6.0-mg/kg TET-exposed animals required more trials to acquire the alleyway task. RAM subjects receiving 6.0 mg/kg of TET were less accurate than those given 3.0 mg/kg or vehicle control. TET did not affect open-field activity on PND10; low levels of spontaneous locomotion occurred regardless of treatment. On PND13, there was a dose-related decrease in locomotion over home-cage litter while all groups exhibited equivalent low rates of locomotion in the absence of home-cage cues. All treatment groups were more active when tested over litter than over no litter. In contrast, on PND21 and throughout the RAM testing period, TET-exposed subjects exhibited dose-related increases in activity. TET produced treatment-related decreases in wet weight of whole brain, hippocampus, and cerebellum in both developing (PND23) and adult (PND200) animals with the hippocampus being most affected on a percentage basis. In contrast, no treatment-related body weight differences were observed at these times. The neurotoxicity of TET can be demonstrated during the preweaning period whether a commonly used endpoint in assessing CNS function (locomotor activity) is monitored or a more complex endpoint (learning) is evaluated provided (1) the method used to monitor locomotor activity incorporates both the normally low levels of preweaning locomotion and the more elevated levels induced by home-cage cues and (2) the learning paradigms utilized are appropriate for the capabilities of the animal.

Triethyltin (TET) is neurotoxic and its administration during the early postnatal period markedly interferes with central nervous system (CNS) development. This disruption is manifested in behavioral, neurochemical, and electrophysiological alterations observed during the entire lifespan of the organism (Dyer *et al.*, 1981; Harry and Tilson, 1981; Reiter *et al.*, 1981; Ruppert *et al.*, 1983; O'Callaghan

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et al., 1983). In the rat a single exposure to TET on Postnatal Day 5 (PND5) results in neurobehavioral effects which include changes in activity (Reiter *et al.*, 1981; Ruppert *et al.*, 1983), deficits in sensorimotor capabilities as well as altered learning ability (Harry and Tilson, 1981), and electrophysiological changes indicative of slowed sensory processing (Dyer *et al.*, 1981). This broad spectrum of neurotoxic effects makes TET an ideal compound with which to evaluate the utility of tests designed to assess the functional integrity of the neonate or juvenile animal after early perinatal insult. Tests designed to detect neurotoxicity during any period of the lifespan should include evaluations of a range of CNS functions (Adams and Buelke-Sam, 1981). However, most evaluations of neurotoxicity during early developmental periods have utilized the endpoints of physical maturation or reflex and motor development (e.g., Maker *et al.*, 1975; Vorhees *et al.*, 1979). In general, learning or memory paradigms are used to assess the impact of early neurotoxic insult on the mature adult rather than on the neonate or juvenile animal (e.g., Harry and Tilson, 1981).

The limited sensory and response capabilities of the neonate make it difficult to evaluate learning and other complex CNS functions during the preweaning developmental period. However, tests structured to the capabilities of the young animal used in conjunction with home-cage cues make such evaluations possible. Faster learning and retention of response contingencies, as well as increases in spontaneous alternation and activity, are obtained if appropriate paradigms are used to evaluate the functional capabilities of the neonate (Smith and Spear, 1978). The present research demonstrates that with the use of suitable tests the developmental perturbation produced by early postnatal exposure to TET is evident during both the preweaning and juvenile developmental periods whether a commonly utilized functional endpoint (e.g., locomotor activity) or a more complex CNS function (e.g., learning) is evaluated.

METHODS

Animals. Gravid Long-Evans rats (Blue Spruce Farms, Altamont, N.Y.) were obtained on Day 2 of gestation and housed individually in plastic tub cages (45 × 25 × 20 cm) with wood shavings as bedding. Pups born between 1700 and 0500 hr were considered to be born on the same day (Day 0). On PND1 pups were reassigned to litters such that each dam received four male and four female pups and no more than one male and one female of her own offspring. Litter was not changed from PND5 to PND16. At 21 days of age littermates were weaned, separated by sex, and housed four per cage. Animals were maintained in a temperature- (22 ± 2°C) and humidity- (50 ± 10%) controlled colony room on a 12:12-hr light:dark cycle beginning at 0600 hr.

Dosing. Intraperitoneal injections of 0.0, 3.0, or 6.0 mg/kg of triethyltin bromide (Alfa Products, Danvers, Mass.) with saline (0.9%) as the vehicle control (10 μl/g body wt) were given on PND5; dose levels are expressed as the salt. The doses used were based on previously published work with this compound (see Ruppert *et al.*, 1983). All animals in a litter received the same dose and were foot tatooed with India ink for later identification. To control for possible test–retest interactions, animals were evaluated in only one test paradigm. A limited number of randomly chosen animals (no more than one or two of each sex) from a litter was used; the remaining animals were removed for biochemical evaluation (see O'Callaghan *et al.*, 1983).

Preweaning Indices

Open field. Separate groups (n = 24) comprised of two males and two females from six litters at each dose and age were tested at 10 and 13 days of age for open-field locomotion in the presence or absence of their own home-cage litter. The apparatus was constructed of clear Plexiglas (25-cm high, 21-cm wide, and 48-cm long) with a steel mesh floor placed over a 2-cm deep Plexiglas pan. The open field was demarcated into a 3 × 4 matrix of 7 cm (i.e., the length of a 10- to 13-day-old pup) squares. The bedding pan was either empty or filled to immediately below the mesh floor with litter (900 ml). Separate open fields were used in the two test conditions and the entire apparatus was placed in a covered 10-gal aquarium to minimize ambient noise and odor. Each animal was placed in a 1000-ml plastic beaker for 10 sec prior to the start of testing and between conditions. Order of testing was counterbalanced across groups and sex. Animals were weighed immediately prior to testing which began with the placement of the pup in the center of the open field with its body straddling a line. Squares crossed were observed for 3 min in each condition, and a count was recorded each time the front paws crossed a line. The wire mesh floor allowed substantial forward locomotion especially on PND13 and pivoting was rarely observed. Interobserver reliability ratings of .90 were obtained for the two observers prior to the start of the study.

Alleyway. On PND13 pups were tested in an appetitive alleyway task (Amsel *et al.*, 1979). However, the procedure was modified to insure treated animals were not debilitated by the testing conditions. The reinforcer was access to home-cage litter and littermates rather than nonnutritive suckling on an anesthetized dam. Animals were separated from the litter for 1 rather than 8 hr. One male and one female per litter were evaluated (n = 10 and 12 for 0.0- and 6.0-mg/kg TET-exposed groups, respectively).

Test procedure. During testing the home cage was maintained at approximately 33°C by a commercial heating pad. A pup was removed from the home cage approximately 1 hr before testing and maintained in an incubator (33°C); the dam was kept in a different room during separation and testing. The Plexiglas apparatus consisted of a 38 × 7.5 × 10-cm alleyway and a 17 × 25 × 10-cm goalbox (GB); the rear of the GB was wire mesh. Testing included aquisition, performance, and extinction phases. The first trial was initiated with two GB placements: first, a 10-sec confinement in an intertrial interval (ITI) chamber and second, placement into the GB immediately followed by 30-sec access to litter and littermates. During acquisition, litter odors were provided in the alleyway by tilting the home cage against the wire end of the GB so "homing" could facilitate the acquisition of the response. A pup was placed in the start area facing away from the GB and given 120 sec to traverse the distance. If the response did not occur within the required time, the pup was pushed to the GB. A GB entrance was followed by 30 sec access to the homecage. Acquisition trials continued until a criterion of five consecutive trials in less than 120 sec was reached. The alleyway was wiped between trials.

The performance phase consisted of 15 consecutive trials with a 10-sec ITI in which the reinforcement conditions were identical to those of the acquisition phase but the odor cues in the alleyway were eliminated. During extinction the pup was confined to the goalbox for 30 sec and not given access to the home cage. Extinction trials continued until two consecutive trials occurred in which the GB was not reached within 60 sec.

Postweaning Indices

Motron. Equal numbers of male and female pups (n = 12/group, 2 males and 2 females/litter) were tested in an automated activity monitoring device early in the juvenile period on PND21. Dams were removed in the early morning, and pups were tested between 1300 and 1600 hr. Motor activity was recorded in six commercial photocell devices (Motron Electronic Motility Meters, Motron Products, Stockholm, Sweden). Each consisted of a platform with a matrix of 40 photocells that were illuminated by a single overhead incandescent lamp (GE 30R20, 30 W). Any horizontally directed movement that interrupted a photocell was recorded and will be referred to as locomotion. A Plexiglas chamber (33 × 21 × 26 cm), placed on top of the platform, was used to contain the rats and had a removable lid. Each entire chamber and photocell apparatus was placed in a wooden enclosure that was lined with acoustically absorbent ruber (FM11, Southern Kinetics, Raleigh N.C.) and equipped with an exhaust (Rotron WR2A1, Woodstock, N.Y.). The six chambers and enclosures were housed permanently in a small test room (5 × 11 × 10 ft) that was lined with acoustic tile. Data collection was carried out in an adjacent room with an Intel 80/80 microprocessor. Rats were tested individually for a 25-min session with photocell interruptions recorded in 5-min blocks.

Radial-arm maze (RAM). Animals (3 males and 3 females/group, randomly selected from different litters) were tested for learning and memory in an automated RAM during the juvenile period (from PND37 through PND53). The automated RAM allows a simultaneous determination of performance accuracy and activity and is described in detail elsewhere (see Miller *et al.*, 1982). Briefly, 24 LED-photodiode pairs, located directly in front of the entrance to each arm, 5 cm into the arm, and in the food cup at the end of each arm, monitored movement. A Gerbrands feeder dispensed 45-mg Noyes pellets directly into the food cup. The operation of the doors and pellet dispensers as well as the recording of the time and location of photodiode interruptions was controlled by a Northstar "Horizon" computer. The criterion for an arm selection was the following sequence of photodiode interruptions: center, arm, and food cup. The RAM, elevated 70 cm above the floor, was located in a well-lighted 110 ft^2 room with distinguishing characteristics on several of the walls.

Animals were allowed access to Purina rat chow in their home cage for approximately 2 hr following daily testing; this schedule allowed adequate deprivation but also ensured growth. Tap water was available *ad libitum* in the home cage. During the first test phase, each cup was baited with a 45-mg Noyes pellet. An interruption of the food cup photocell resulted in the immediate presentation of an additional pellet for a possible total of 16 pellets per session. Phase 2 started the day after an animal had entered all the arms and eaten all pellets. During the 14 days of the second phase, pellets were available only when the photocell in the feeder cup was interrupted, reducing the possible pellets per session to eight. On the final test day, no pellets were available in any alley (i.e., extinction). A daily session (Mon–Fri) was 10-min long; arm selections could be made the entire time, but only the first eight correct selections were reinforced.

Brain and body weight. Wet weight of whole brain and areas known to have significant postnatal development, the hippocampus and cerebellum (Altman and Das, 1965;

Pellegrino and Altman, 1979), were obtained on PND23 from animals not used for behavioral testing and from the RAM animals following retesting at 190 to 200 days of age (RAM retest data not presented here). Body weights were also measured at the time of testing.

Statistical analyses. For tests with several measurements on the same subject (e.g., RAM) data were analyzed by a multivariate general linear model (Morrison, 1967); all MANOVAs indicated no significant effect of sex of the subject so data for males and females were combined in all subsequent analyses. When significant differences (Wilk's criterion used throughout) were found, individual variables were analyzed by ANOVA. When significant interactions with the within-subjects factor were found for repeated measures ANOVA (Keppel, 1973), simple main effects were examined at each level of the repeated factor. For tests with a single measurement, only ANOVAs were performed. F values greater than those associated with the critical value at $p > 0.05$ were accepted as significant. Post hoc individual mean comparisons were made with Duncan's multiple range test. Details of the statistical evaluation for a particular measure appear in the figure legend.

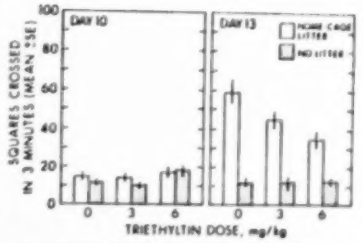

FIG. 1. Open-field activity over no litter and home-cage litter for separate groups of animals at 10 and 13 days of age as a function of dose (0.0, 3.0, or 6.0 mg/kg, ip) on PND5. A repeated measure ANOVA showed all main effects for locomotion were nonsignificant on PND10. A repeated measure ANOVA of locomotion on PND13 indicated a treatment × condition interaction ($F(2,57) = 8.98$, $p < .0004$). Treatment effects were found only in the home-cage litter condition ($F(2,57) = 8.45$, $p < .0006$). The 6.0-mg/kg TET-exposed group crossed fewer squares than the 3.0- or 0.0-mg/kg TET-exposed groups.

RESULTS

Preweaning Indices

Open field. Preweaning locomotion was altered by postnatal TET treatment, but the decreases observed were dependent on age and test condition (Fig. 1). Uniformly low rates of spontaneous locomotion were observed on PND10 in both test conditions. In contrast, the groups tested on PND13 were more active over home-cage litter than no litter indicating home-cage litter is activating at this age (see Smith and Spear, 1978). However, more pertinent to this study is the TET-related decrease in locomotion over home-cage litter; the 6.0-mg/kg animals crossed significantly less squares than either the control or 3.0-mg/kg animals. Thus treatment effects were not observed during periods of low rates of spontaneous locomotor activity but were apparent only when locomotion was increased in the presence of home-cage cues. Treatment also affected body weight on PND10, $F(2,54) = 9.00$, $p < .0004$; the 6.0-mg/kg group (21.4 g) was lighter than either the 3.0-mg/kg group (23.6 g) or the 0.0-mg/kg group (25.3 g). Weight did not differ on PND13 (30.1, 28.9, and 28.8 g for the 0.0-, 3.0-, and 6.0-mg/kg TET-exposed groups, respectively).

Alleyway. Postnatal administration of TET impaired learning ability; the TET-treated animals required more trials than controls to acquire the alleyway response (5.6 vs 8.3; $t(14,5) = 2.370$, $p < 0.0322$). This impairment is also reflected in the time required to reach the goalbox during acquisition; the treated animals were always slower (Fig. 2). In contrast, performance was equivalent during the performance phase. Thus, TET affected the acquisition of the task but did not affect the ability to perform the response once it was acquired. Early TET exposure did not, however, interfere with extinction of the response when the reward was removed; both groups required approximately the same number of trials to reach the extinction criterion (23.5 vs 23.4 trials for the 0.0- and 6.0-mg/kg TET-exposed groups, respectively). The groups did not differ in body weight.

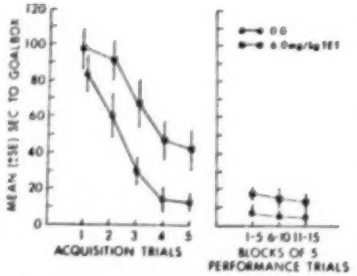

FIG. 2. Acquisition and performance of a linear alleyway response on PND13 as a function of dose (0.0 or 6.0 mg/kg, ip.) on PND5. Home-cage cues of litter and littermates were used as the reinforcer. A repeated measure ANOVA indicated significant treatment ($F(1,22) = 4.92$, $p < .0371$) and trial ($F(4,88) = 25.59$, $p < .0001$) effects during acquisition but no interaction between these variables. No statistically significant effects were found during the performance phase.

Postweaning Indices

Motron. In contrast to the decreases in locomotion found during the preweanling period, activity increases were observed during the postweaning period. The 6.0-mg/kg TET-exposed animals were more active than either of the other groups (Fig. 3). Photocell interruptions decreased throughout the course of the 25-min test period and although the 6.0-mg/kg TET-exposed group was always more active, treatment did not interfere with this pattern of habituation. No differences in body weight were observed (50.1, 50.0, and 50.4 g for the 0.0-, 3.0-, and 6.0-mg/kg TET-exposed groups, respectively.

RAM. The effect of TET on RAM performance was assessed with the following dependent variables which can be classified generally as indicators of accuracy: (1) unrepeated arm selections in the first eight choices, (2) total arm selections required to obtain eight pellets; or activity: (1) photocell interruptions, (2) total arm selections in a daily session. Only Phase 2 data are presented since TET did not affect the number of days required to enter and eat in all arms (1.5, 1.5, and 1.6 days for the 0.0-, 3.0-, and 6.0-mg/kg TET-exposed groups, respectively).

(a) Accuracy. Early neonatal exposure to TET severely comprised the ability of the 6.0-mg/kg group to obtain all the pellets as efficiently as the other groups (Fig. 4). The 6.0-mg/kg TET-exposed group reentered arms already chosen resulting in more errors and fewer correct selections in the first eight choices. Continued experience with the RAM resulted in more efficient performance but the 6.0-mg/kg TET-treated animals were always less accurate.

(b) Activity. Consistent with the hyperactivity observed in the Motron, a persistent dose-related hyperactivity was observed throughout the RAM test period for both indices of activity (Fig. 5). In contrast to the activity increases observed only in the 6.0-mg/kg group in the Motron, both the 3.0- and 6.0-mg/kg groups were more active than controls in the RAM.

(c) Extinction. The nonreward of an unrepeated arm selection does not interfere with

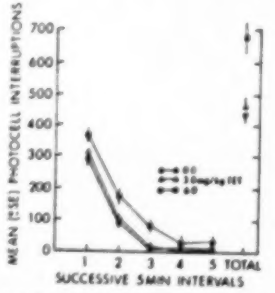

FIG. 3. Activity (photocell interruptions) in the Motron expressed as mean interruptions for the consecutive 5-min intervals of the 25-min session and mean total interruptions as a function of dose (0.0, 3.0, or 6.0 mg/kg, ip) on PND5. A repeated measure ANOVA showed an effect of treatment ($F(2,33) = 9.11$, $p < .0007$) and interval ($F(4,132) = 200.69$, $p < .0001$) but no treatment × interval interaction.

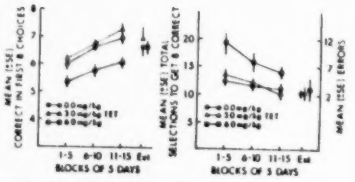
MEAN (±SE) CORRECT IN FIRST 8 CHOICES
MEAN (±SE) TOTAL SELECTIONS TO GET 8 CORRECT
MEAN (±SE) ERRORS
0.0 mg/kg
3.0 mg/kg TET
6.0 mg/kg
1-5 6-10 11-15 Ext
BLOCKS OF 5 DAYS

FIG. 4. Accuracy in the RAM expressed as mean correct choices in the first eight choices and total choices needed to select eight different arms for Phase 2 and the day of extinction (EXT) as a function of dose (0.0, 3.0, or 6.0 mg/kg, ip) on PND5. A repeated measure ANOVA showed an effect of treatment ($F(2,13) = 27.45$, $p < .0001$) and blocks ($F(2,26) = 15.76$, $p < .0001$) for the correct choices in the first 8 choices and an effect of treatment ($F(2,13) = 11.78$, $p < .0012$) and blocks ($F(2,26) = 5.95$, $p < .0075$) for the total choice measure. The 6.0-mg/kg TET-exposed group required more choices than either the 3.0- or 0.0-mg/kg TET-exposed groups for either measure of accuracy. A repeated measure ANOVA comparing the last block of Phase 2 and the day of EXT did not show any dose-dependent differences.

accuracy; all groups were at least as accurate during extinction as during rewarded testing (Fig. 4). In fact, the 6.0-mg/kg TET-exposed group appeared to improve when correct choices were not rewarded, but this result may be a function of their pronounced decrease in activity during extinction. The effects of nonreward on activity were dependent on treatment (Fig. 5). The control group showed an increase in activity while both TET-exposed groups showed decreases. However, the drop was more pronounced for the 6.0-mg/kg TET-treated group.

Brain weight. Postnatal TET produced treatment-related decreases ($n = 6$ for all measures) in wet weight of whole brain on PND23 (1.58, 1.514, and 1.275 g for the 0.0-, 3.0-, and 6.0-mg/kg TET-exposed groups, respectivelv) and in adults (2.157, 2.017, and 1.639 g for 0.0-, 3.0-, and 6.0-mg/kg TET-exposed groups, respectively). Weight of the hippocampus was affected at PND23 (0.100, 0.087, and 0.064 g for the 0.0-, 3.0-, and 6.0-mg/kg TET-exposed groups, respectively) and in the adult (0.108, 0.096, and 0.067 g for 0.0-, 3.0-, and 6.0-mg/kg TET-exposed groups, respectively). Cerebellar weight decreases were also found on PND23 (0.220, 0.201, and 0.185 g for the 0.0-, 3.0-, and 6.0-mg/kg TET-exposed groups, respectively) as well as in the adult (0.315, 0.296, and 0.265 g for 0.0-, 3.0-, and 6.0-mg/kg TET-exposed groups, respectively). There were no body weight differences at either age. Similar changes in brain weights as a function of early postnatal exposure to TET have been reported with a different strain (albino) and a slightly different dosing regimen (see Reiter *et al.*, 1981; Ruppert *et al.*, 1983).

DISCUSSION

The neurotoxic effects of acute postnatal administration of TET were manifest early in development by learning deficits and altered motor behavior. That pronounced neurobe-

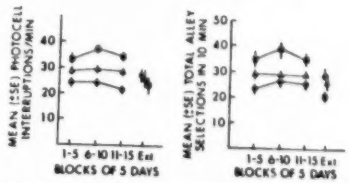

FIG. 5. Activity in the RAM expressed as mean photodiode interruptions/min and total alley choices in a 10-min session for Phase 2 and the single day of extinction (EXT) as a function of dose (0.0, 3.0, or 6.0 mg/kg, ip) on PND5. A repeated measure ANOVA showed an effect of treatment for photocell interruptions ($F(2,13) = 6.95$, $p < .0089$) and total alley choices ($F(2,13) = 5.82$, $p < .0157$). Dose-related increases in activity were manifest throughout testing. A repeated measure ANOVA comparing the last block of Phase 2 and the single day of EXT showed no dose-related changes in total photocell interruptions but separate ANOVAs indicate there was a significant difference in activity during the last block ($F(2,13) = 6.35$, $p < .0110$), but not during EXT. A comparison of the last block of Phase 2 and EXT for total choices indicated an interaction between treatment and test condition ($F(2,13) = 11.97$, $p < .0011$). Separate ANOVA's indicate the treatment effect observed on the last block of Phase 2 ($F(2,13) = 5.58$, $p < .0178$) was reduced by the removal of the reinforcer ($F(2,13) = 3.16$, $p < .0760$).

havioral changes were still observed during the juvenile period suggest that the CNS functional alterations induced by TET are persistent and may be permanent. The present study demonstrates that paradigms tailored to the limited capabilities of the neonate can be used to determine functional competence in immature rats and thus provide the means for assessing the neurotoxicity of other compounds during early development in this species. Whether neonatal tasks tailored to the response capabilities of other species, including humans, will be useful in the detection and characterization of neurotoxicity should be determined. In this regard, human neonates display altered physical development and later reduced intellectual capacity after exposure to certain neurotoxicants (e.g., alcohol, methyl mercury) (Clarren and Smith, 1978; Darby *et al.*, 1981; Reuhl and Chang, 1979). Human infants exposed to alcohol *in utero* are reported to be irritable and tremulous and to display weak sucking ability during the early developmental period (Clarren and Smith, 1978). These reported alterations in behavior suggest it may be possible to use neurobehavioral tasks as well as physical indices to assess and characterize toxicity in human neonates. In addition to the detection and characterization of neurotoxicity, appropriate tests of function in the neonate may be useful in determining whether early deficits are related to or predictive of later disturbances. However, the limited neonatal capabilities of most species with the attendant assessment difficulties have precluded any extensive experimental validation of this concept (see Adams and Buelke-Sam, 1981).

Postnatal TET exposure caused perturbations in the motor activity of both the neonate and juvenile rat and these findings again reinforce the idea that alterations in the activity of an organism may be a sensitive index of altered CNS function (Grant, 1976; Reiter and MacPhail, 1982).

Although locomotor activity is clearly affected after early postnatal exposure to TET, it is difficult to draw firm conclusions regarding TET's specific effects on locomotor activity during the preweaning period. For example, Reiter and colleagues (1981) reported that TET did not affect the development of open-field activity, but behavior was not monitored in the presence of home-cage cues and activity levels were low. In contrast, they found a retarded motor development when some aspect of the home environment was included in testing. Delays in locomotor development following early TET exposure are also suggested by the present data. Thus, it appears that a preweaning activity task in which both low and moderate levels of locomotion can be obtained is best suited for the detection of perturbations during this early developmental stage. That a compound's effects on a specific behavior can be determined in part by the baseline rate of that behavior has been repeatedly demonstrated (e.g., Clark and Steele, 1966; Leander, 1975).

Motor ability of untreated rats gradually improves during the period of most active myelination (Davison and Dobbing, 1966; Jacobson, 1963). TET is known to produce vacuolization and splitting of myelin in adult rats (Suzuki, 1971) and exposure to TET during the early postnatal period induces biochemical alterations suggestive of perturbation in the myelination process (O'Callaghan *et al.*, 1983). However, the notion that the activity changes observed in this study, which include both preweaning motor deficits and persistent increases in adult activity, are solely the result of a TET-induced myelin deficit is unlikely. TET's extensive effects on pre- and postweaning activity are more likely a reflection of insult to a number of different brain structures or systems through either an interference with processes occurring during the postnatal developmental period, such as synaptogenesis and myelinogenesis, or direct cell toxicity.

The treatment-related increases in activity exhibited in both the Motron and RAM during the postweaning period replicate and extend previous work characterizing the developmental neurotoxicity of TET (Harry and Tilson, 1981; Reiter *et al.*, 1981; Ruppert *et al.*,

1983). These data indicate that early postnatal TET exposure produces persistent changes in activity which include a pervasive hyperactivity, evident at weaning and demonstrable in a variety of monitoring devices.

The RAM has proven sensitive to hippocampal dysfunction (Jarrard, 1978; Olton *et al.*, 1979) and effective in identifying learning deficits following preweaning treatments known to affect both hippocampal morphology and function (Petit *et al.*, 1983; Taylor *et al.*, 1982). Despite the persistent, treatment-related decreases in hippocampal weight reported here, it is doubtful that the learning deficits obtained after postnatal TET exposure are mediated solely through a selective interference with development of the limbic system in general, or the hippocampus specifically. First, the present study as well as other work (Ruppert *et al.*, 1983) shows that TET produces persistent weight decreases in other brain areas, not just the hippocampus. Second, functions in other brain systems or areas contribute to preweaning learning capacity (Sahley and Nonneman, 1979). Third, TET has been reported to alter electrophysiological endpoints in a manner indicative of slowed sensory processing (Dyer *et al.*, 1981). Damage to brain areas involved in processing and utilization of visual or sensory information is known to disrupt RAM performance (Dean and Key, 1981). Thus, the alterations in learning induced by acute postnatal TET exposure may reflect a generalized neurotoxicity rather than relatively specific hippocampal damage.

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